

Application No. 10/627,483  
 Reply to Office Action of March 30, 2005

RECEIVED  
 CENTRAL FAX CENTER  
 JUN 23 2005

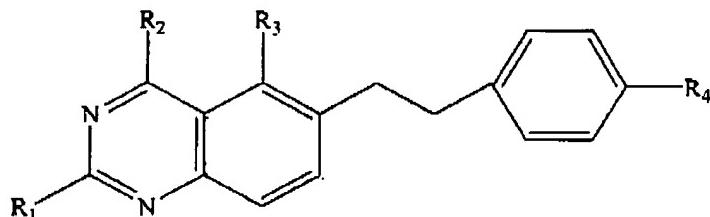
**Amendments to and Listing of the Claims:**

Please amend the claims as set forth in the following listing of claims, which replaces all prior claim listings:

1. and 2. (Cancelled)

3. (Currently Amended) In a process for synthesizing a compound of formula Ib:

(Ib)



wherein R<sub>1</sub> and R<sub>2</sub> are each individually amino or N-alkyl substituted amino; hydroxy; alkoxy; keto; lower alkyl; ~~or a nitrogen or oxygen protecting group;~~

R<sub>3</sub> is hydrogen; hydroxy; alkoxy; trifluoromethyl alkoxy; halo; sulphydryl or alkylthio;

R<sub>4</sub> is -C(O)-X;

X is hydroxy; alkoxy; or γ-methylene glutamic acid, glutamic acid, aspartic acid, or γ-methylene glutamate an amino acid residue;

in which process a 2-amino-5-nitro-benzonitrile starting reagent is cyclized to form 2,4-diamino-6-nitro-quinazoline, which is converted to 2,4,6-triamino-quinazoline, which is converted to 2,4-diamino-6-cyano-quinazoline, which is converted to 2,4-diamino-6-formyl-quinazoline;

the improvement comprising:

reacting a bromo-alkyl an R<sub>4</sub>-p-benzoic acid alkylene moiety with triethyl phosphite to form a 4-R<sub>4</sub>-carbonyloxyalkyl-phenyl-alkyldiethylphosphiteonate; and

reacting the 2,4-diamino-6-formyl-quinazoline with the 4-R<sub>4</sub>-carbonyloxyalkyl-phenyl-alkyldiethylphosphiteonate to form a product with an unsaturated bond; and to form the compound of formula Ib.

reducing said product to form the compound of formula Ib.

Application No. 10/627,483  
Reply to Office Action of March 30, 2005

4. (Currently Amended) The process of claim 3, wherein the product with an unsaturated bond an R<sub>4</sub>-p-benzoic acid alkylene moiety is a methylene moiety.

5. (Currently Amended) The process of claim 4, wherein the R<sub>4</sub>-p-benzoic-acid methylene moiety is 4-(bromo 1,2-methylene)benzoate.

6. (canceled)

7. (canceled)

8. (Currently Amended) The process of claim 3, wherein the 4-R<sub>4</sub>-carbonyloxyalkyl-phenyl- alkyldiethylphosphiteonate is 4-carbonyloxymethyl-phenyl- methyldiethylphosphiteonate.

9. (previously presented) The process of claim 3, further comprising hydrogenating the compound of formula Ib to form 6-(4-R<sub>4</sub>-carbonyloxyalkylphenyl)ethanyl-2,5-diamino quinazoline, which is hydrolyzed to form 6-(4-R<sub>4</sub>-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline,

the improvement further comprising:

reacting 6-(4-R<sub>4</sub>-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with diethyl  $\gamma$ -methylene-L-glutamate to form  $\gamma$ -methylene glutamate 5,8,10-trideaza aminopterin diethyl ester.

10. (previously presented) The process of claim 9, wherein the improvement further comprises reacting the 6-(4-R<sub>4</sub>-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with the diethyl  $\gamma$ -methylene-L-glutamate in the presence of 1-hydroxy benzotriazole and 1-[3-dimethylamino]propyl]-3-ethyl carbodiimide hydrochloride.

11. (previously presented) The process of claim 9, wherein the improvement further comprises reacting the 6-(4-R<sub>4</sub>-carbonyloxyphenyl)ethanyl-2,5-diamino quinazoline with the diethyl  $\gamma$ -methylene-L-glutamate in the presence of 1-hydroxy benzotriazole, 1-[3-dimethylamino]propyl]-3-ethyl carbodiimide hydrochloride and triethylamine.